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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,450	09/15/2003	Merja E. Penttila	GC590-2-C1	2737

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EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/663,450	PENTTILA ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	maf

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,26-34,36,83-85 and 87-95* is/are pending in the application.

4a) Of the above claim(s) *83-85 and 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,26-34,36,83-85 and 87-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/15/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 10/17/2005 in which claim 29 was amended; claims 14-25, 37-82 and 86 were cancelled; claims 83-85 and 87 were withdrawn; and claims 88-95 were added. Claims 1-13, 26-34, 36, 83-85 and 87-95 are pending.

Election/Restrictions

Applicant's election of Group I (claims 1-13, 26-34 and 36) in the reply filed on 10/17/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is deemed proper and is therefore made FINAL.

Information Disclosure Statement

The information disclosure statement filed 9/15/2003 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused

it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Specification

The disclosure is objected to because of the following informalities: the Figure 10 description on page 10 does not include a SEQ ID number for the yeast sequence provided. Figure 16 also contains three sequences for which there are no SEQ ID numbers either on the drawing or in the figure legend.

Appropriate correction is required.

Claim Objections

Claim 1 is objected to because of the following informalities: claim 1 recites "from a yeast or a filamentous fungi" and should read "from a yeast or a filamentous fungus".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4, 26-27, 29, 36, 88-90 & 95, and therefore dependent claims 3, 5-13, 28, 30-34 & 91-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "the parental cell" in lines 6-7. Claim 1 is vague and indefinite in that there is no antecedent basis for the parental cell.

Claim 1 recites "A method of increasing the secretion of a heterologous protein in a eukaryotic cell comprising inducing an elevated unfolded protein response (UPR) by increasing the presence of a UPR-modulating protein isolated from a yeast or a filamentous fungi" in lines 1-3. Claim 1 is vague and indefinite in that it is not clear whether the UPR-modulating protein must first be isolated from a yeast or filamentous fungus and then transformed into a eukaryotic cell or whether the UPR-modulating protein need only be derived from and/or present in the yeast or filamentous fungus (eukaryotic cell) from which the heterologous protein is secreted.

Claims 1 and 88-90 also recite "a DNA binding domain that has at least 70%/80%/90%/95% similarity to a DNA binding domain set forth in Figure 10." Claims 1 and 88-90 are vague and indefinite in that it is unclear which DNA binding domain is

referred to, e.g. the DNA binding domains consisting of residues 84 to 147 of SEQ ID NO: 5 and residues 53 to 116 of SEQ ID NO: 6, or are there other DNA binding domains within the sequences set forth in Figure 10?

Claim 2 recites "wherein inducing is by increasing the presence of HAC-1 protein in said cell." Claim 2 is vague and indefinite in that it is unclear what is being induced: the UPR or the presence of a UPR-modulating protein or both?

Claims 2, 26-27, 29 and 36 recite "[t]he method of claim 1 wherein...said cell." Claims 2, 26-27, 29 and 36 are vague and indefinite in that "said cell" may refer either to the parental cell or the eukaryotic cell of claim 1.

Claim 4 recites "by a UPR inducing form of a HAC1 recombinant nucleic acid" in lines 1-2. What are the metes and bounds of a UPR inducing form of a HAC recombinant nucleic acid? Does such a nucleic acid include any "nucleic acid which has been modified to give rise to a translatable mRNA" (page 22 of the instant specification) or is such a nucleic acid limited to those comprising "a sequence consisting essentially of coding sequence" (ibid) or only to nucleic acids which encode truncated HAC1?

Claim 95 recites "and the heterologous protein is selected from the group of proteases, cellulose, glucoamylase, alpha

amylases and combination thereof" in lines 3-5. Claim 95 is vague and indefinite in that it is unclear whether the group consists of or comprises proteases, cellulose, glucoamylase, alpha amylases and combination thereof.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 88-90, and therefore dependent claims 2-13, 26-34, 36, and 91-95, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to UPR-modulating proteins isolated from yeast or filamentous fungi, wherein the UPR-modulating protein comprises a DNA binding domain that has at least 70% (claim 1), 80% (claim 88), 90% (claim 89) and 95% (claim 90) similarity with a DNA binding domain set forth in Figure 10.

The claims encompass any UPR-modulating protein (including mutants, chimeric proteins, etc.) isolated from any yeast or any filamentous fungi with a DNA binding domain set forth in Figure 10 or with a DNA binding domain with at least 70% similarity to a DNA binding domain set fort in Figure 10. The claims do not provide any structural information with regard to the DNA binding domain sequences set forth in Figure 10. Thus, the rejected claims comprise a set of amino acid sequences that are defined by the function of the encoded protein.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes HAC1/hacA proteins from four different species of yeast or filamentous fungi: *Saccharomyces cerevisiae, Trichoderma reesei, Aspergillus niger,* and *Aspergillus nidulans;* and the approximate sequences of DNA binding domains for three of the above named species: *T. reesei, A. niger* and *A. nidulans* (see entire document, especially last paragraph on page 19). No description is provided of those residues within the identified

DNA binding domains which are essential for DNA binding; neither are any motifs described which would allow one of skill in the art to identify UPR-modulating proteins with DNA binding domains with even 95% similarity to one of the DNA binding domains set forth in Figure 10.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of four UPR-modulating proteins comprising a DNA binding domain set forth in Figure 10. The results are not necessarily predictive of any other amino acid sequences comprising a UPR-modulating protein comprising a DNA binding domain 70%-95% similar to a DNA binding domain set forth in Figure 10. Thus it is impossible to extrapolate from the example described herein those amino acid molecules that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe any other UPR-modulating proteins isolated from yeast or filamentous fungi comprising a DNA binding domain set forth in Figure 10 or comprising a DNA binding domain with 75%, 80%, 90% or 95% similarity to a DNA binding domain set forth in Figure 10.

Schröder et al teach in an article published after the filing date of the current invention that the only known UPR pathway in yeast is that which originates with Ire1p which in turn activates the transcription factor HAC1 (Schröder, M. et al, Molecular Microbiology 49(3):591-606, 2003; see entire document, especially pg. 591, last paragraph).

Given the very large genus of amino acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the chimeric sequences capable of fulfilling the claim limitations of claims 1 and 88-90, the skilled artisan would not have been able to describe the broadly claimed genus of UPR-modulating proteins isolated from yeast or filamentous fungi comprising a DNA binding domain with at least 75%, 80%, 90% or 95% similarity to a DNA binding domain set forth in Figure 10. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those amino acid sequences that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention.

Claims 1 and 88-90, and therefore dependent claims 2-13, 26-34, 36, and 91-95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for HAC1/hacA isolated from *S. cerevisciea*, *T. reesei*, and *A. niger var. awamori* used in conjunction with certain secreted heterologous proteins, does not reasonably provide enablement for *A. nidulans* HAC1 or any other UPR-modulating protein comprising a DNA binding domain set forth in Figure 10 or comprising a DNA binding domain with 70%, 80%, 90% or 95% similarity with a DNA binding domain set forth in Figure 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected claims are drawn toward a method of increasing the secretion of a heterologous

protein in a eukaryotic cell comprising inducing an elevated unfolded protein response (UPR) by increasing the presence of a UPR-modulating protein isolated from yeast or filamentous fungi comprising a DNA binding domain that has at least 70% similarity (claim 1), 80% similarity (claim 88), 90% similarity (claim 89) or 95% similarity (claim 90) to a DNA binding domain set forth in Figure 10. The invention is complex in that it involves any stimulus for increasing the presence of a UPR-modulating protein with the recited limitations, the concurrent heterologous expression of a protein which is secreted and the manipulation of the unfolded protein response such that the secretion of the heterologous protein is increased by increasing the presence of the recited UPR-modulating protein. Increasing the presence of a UPR-modulating protein is not simply a matter of expressing any form of a UPR-modulating protein. For example, endogenous HAC1 protein amount is only expressed after a 252 nucleotide intron is spliced from the HAC1 mRNA and this requires an unconventional tRNA ligase-dependent pre-mRNA splicing event (Shamu, C, Splicing: HACking into the unfolded-protein response, Current Biology, 8:R121-R123, 1998; see entire document, especially page R121, third and fourth paragraphs).

Breadth of the claims: The claims are very broad in that they encompass any UPR-modulating protein isolated from a yeast

or filamentous fungi comprising a DNA binding domain that is 70% similar to a DNA binding domain set forth in Figure 10. The claims include any recombinant and/or mutant proteins comprising a DNA binding domain with 70% similarity to one set forth in Figure 10.

Guidance of the specification/The existence of working examples: The specification teaches that secretion of a heterologous protein can be increased by expression of a UPR inducing form of a HAC1 recombinant nucleic acid. There are two working examples in the specification of methods for increasing the secretion of a heterologous protein comprising inducing a UPR by increasing the presence of a UPR-modulating protein isolated from yeast or filamentous fungi: Examples 7 & 9 describe how increased HAC1 isolated from *T. reesei* increases the secretion of heterologous alpha-amylase and chymosin, respectively; Example 12 describes how hacA from *A. niger var. awamori* increases the secretion of heterologous laccase and/or preprochymosin. No specific teachings are provided with regard to inducing other UPR-modulating proteins isolated from yeast or filamentous fungi comprising a DNA binding domain with 70% similarity to a DNA binding domain set forth in Figure 10 wherein the induction of the elevated UPR results in the increased secretion of the heterologous protein.

State of the art: At the time of Applicant's invention, the art of increasing heterologous protein secretion via induction of a UPR-modulating protein isolated from yeast or filamentous fungi comprising a DNA binding domain with at least 70% similarity to a DNA binding domain set forth in Figure 10 was underdeveloped.

Predictability of the art and the amount of experimentation necessary: Clarke et al teach the generation of a reporter gene construct to examine the role of an increase in the IRE1-mediated UPR on heterologous protein expression (J. Cell. Bioch. Suppl. No 19B, 1995, p.209). However, in an article published post-filing of the instant application Valkonen et al (Applied and Environmental Microbiology 69(4):2065-2072, 2003) teach that overexpression of the yeast HAC1 or *T. reesei* hac1 can lead to increased secretion of heterologous alpha-amylase but not heterologous endoglucanase (see entire document, especially the Abstract and Figures 2B and 4B on pages 2068 and 2070, respectively). Valkonen et al also teach that "we still do not completely understand the features of proteins that affect their secretion and what specific problems different proteins may encounter in heterologous hosts" (page 2071, last paragraph). It is clear that one skilled in the art would be required to conduct a number of experiments to determine which UPR-

modulating proteins encompassed by the rejected claims could be used in conjunction with which heterologous proteins in a method to increase heterologous protein secretion in a eukaryotic cell. This unpredictability is exacerbated by the large genus of UPR-modulating proteins comprising a DNA binding domain set forth in Figure 10 or a DNA binding domain with 70%, 80%, 90% or 95% similarity to a DNA binding domain set forth in Figure 10 and the almost limitless list of potentially secreted heterologous proteins.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-7, 26-28 and 88-90, and therefore dependent claims 3, 8-13, 29-34, 36, 91-95 are rejected under 35 U.S.C. 102(b) as being anticipated by Clarke, et al (J. Cell. Bioch. Suppl., no 19B, p. 209, 1995) as evidenced by Shamu (Current Biology, 8:R121-R123, 1998).

Note: For purposes of this anticipation rejection, Examiner has interpreted "isolated from a yeast or filamentous fungi" to mean that the UPR-modulating protein is derived from and/or present in a yeast or filamentous fungus (eukaryotic cell) from which the heterologous protein is secreted (see U.S.C. 35, §112 2nd rejection above).

The invention is drawn to a method of increasing the secretion of a heterologous protein in a eukaryotic cell comprising inducing an elevated unfolded protein response (UPR) by increasing the presence of a UPR-modulating protein isolated from a yeast or filamentous fungus, wherein the UPR-modulating protein comprises a DNA binding domain that has at least 70% similarity to a DNA binding domain set forth in Figure 10, and further wherein the induction of the elevated UPR results in the increased secretion of the heterologous protein (claim 1). Applicant's invention is further drawn to such a method wherein inducing is by increasing the presence of HAC1 protein (claim 2), wherein said increase of HAC1 protein is by a UPR inducing form of a HAC1 recombinant nucleic acid (claim 4), wherein the HAC protein is encoded by a nucleic acid isolated from a cell selected from *Saccharomyces cerevisiae* (claims 5-7), wherein said cell is selected from *S. cerevisiae* (claims 26-28), and wherein said UPR-modulating protein comprises a DNA binding

domain that has at least 80% (claim 88), 90% (claim 89) and 95% (claim 90) similarity to a DNA binding domain set forth in Figure 10.

Clarke et al teach that overexpression or activation of IRE1 in *S. cerevisiae* is involved in increased foreign protein secretion. Clarke et al utilize a reporter gene construct to observe an increased unfolded protein response on heterologous protein secretion upon IRE1 overexpresion or activation. Activation of IRE1 is upstream of HAC1 in the unfolded protein response as taught by Shamu (see entire document, especially Figure 1) and specifically controls the presence of HAC1 protein (a UPR modulating protein with a DNA binding domain with at least 70% similarity to a DNA binding domain set forth in Figure 10). Only active IRE1 causes cleavage of uninduced HAC1 (HAC1u) mRNA into induced HAC1 (HAC1i). Prior to this cleavage event, uninduced HAC1 mRNA is not translated. Thus, activation of IRE1 increases the presence of HAC1 as part of the unfolded protein response and this leads to increased secretion of the foreign protein from an *S. cerevisiae* cell. Because the HAC 1 protein is from *S. cerevisiae* and up-regulated as a result of an increase UPR, the HAC1 protein is increased by a UPR inducing form of a HAC1 recombinant nucleic acid (claim 4), wherein the HAC protein is encoded by a nucleic acid isolated from a cell

selected from *S. cerevisiae* (claims 5-7), wherein said cell is selected from *S. cerevisiae* (claims 26-28), and wherein said UPR-modulating protein comprises a DNA binding domain that has at least 80% (claim 88), 90% (claim 89) and 95% (claim 90) similarity to a DNA binding domain set forth in Figure 10.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter A. Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office.)

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

December 21, 2005

JAMES KETTER
PRIMARY EXAMINER